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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LEFFERS JR, GERALD G	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 04/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/884,875	CHEN ET AL.	
	Examiner	Art Unit	
	Gerald G Leffers Jr., PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10 and 19-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-7 and 19-22* is/are rejected.

7)☒ Claim(s) *2,3,8-10,23 and 24* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of an amendment, filed 12/15/2003, in which several claims were amended (claims 1, 4-7 & 22). Claims 1-10, 19-24 are pending in the instant application.

Response to Amendment

Any rejection of record in the previous office actions not addressed herein is withdrawn. This action is not final as there are new grounds of rejection herein that were not necessitated by applicants' amendment of the claims in the response filed 12/15/2003. Applicants' response indicates that the term "*in vitro*" is intended to refer to both cell-free and cell-based methodologies. Support for this interpretation of the terminology is present in the originally filed claims where at least one dependent claim indicates that the *in vitro* method is practiced in an intact cell (i.e. "within an eukaryotic cell"-original claim 6). Applicants' further assertion that claim 7, reciting that the method is performed using a "sample" comprising RelA, also encompasses cell-based methods is noted.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall

> have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The rejected claims are directed to methods for identifying an agent that modulates NF-kB activity (e.g. in transcription of a gene in a eukaryotic cell). The method comprises detection of a change in the level of deacetylated RelA of the NF-kB heterodimer (i.e. p50/RelA complex) in response to the presence of an agent. The step of detecting the level of deacetylated RelA in a sample can be performed by detecting an increase in RelA binding to IkBα (e.g. claim 6). The term "*in vitro*" is taken, as per applicants' arguments in the response filed 12/15/2003, to encompass both cell-free and cell-based methodologies where the eukaryotic cell is not present in an organism.

The specification teaches that NF-kB is a heterodimeric transcription factor whose activity is tightly regulated in the cytoplasm by its interaction with a family of cytoplasmic inhibitory factors proteins, IkB. The IkBs prevent the nuclear transport of NF-kB by masking the nuclear localization signal present in the RelA protein. Following the signal-coupled degradation of IkB (i.e. phosphorylation- and ubiquitination-mediated), the nuclear localization signal in RelA is unmasked, allowing NF-kB to be rapidly transported into the nucleus where it binds to the DNA at kB sites. DNA binding by the NF-kB complex leads to the recruitment of the p300/CBP and P/CAF co-activators, which participate in activation of target gene transcription. The instant specification teaches that RelA is acetylated by p300 and CBP. According to applicants' model, active NF-kB remains in the nucleus until the RelA subunit is deacetylated by HDAC3. Deacetylated, but no acetylated, RelA is bound effectively by IkBα. The binding of IkBα to deacetylated RelA promotes nuclear export of the RelA containing,

transcription factor complex, thereby terminating the NF-kB-mediated transcriptional response (e.g. pages 8-9 "Overview"). Thus, according to applicants' specification, NF-kB bound to IkB in the cytoplasm necessarily comprises RelA in a deacetylated state. Therefore, detection of an increase in NF-kB/IkB complex in the cytoplasm of a cell in the presence of a particular agent would necessarily satisfy the limitation of detecting an increase in the presence of deacetylated RelA. The specification further teaches that HeLa cells are suitable for use in the screening methodologies encompassed by the rejected claims and that the proposed mechanism for regulation of NF-kB activity is observable in HeLa cells (e.g. paragraph 0085; Example 1).

With regard to claim 7, a reasonable interpretation of the term "sample" is that it encompasses a cell comprising RelA and the other elements recited in claim 7 and dependent claims that do not limit the method to a cell-free embodiment. With regard to the limitation of claim 19 that the contacting step is done in the "presence" of a protein or protein complex that acetylates RelA, the claim is read broadly to encompass a sample where the protein or protein complex is in the same cell as the RelA protein (e.g. as recited in claim 21).

Claims 1, 4-7 & 19-22 are rejected under 35 U.S.C. 102(e) as being anticipated by Karin et al (U.S. Patent No. 6,242,253 B1; see the entire patent). **This is a new rejection.**

Karin et al teach the cloning of genes encoding a pair of kinases and the characterization of their activity with regard to IkB phosphorylation and NF-kB activities (e.g. the Abstract). Karin et al teach the characterization of both wildtype (i.e. IKKα and

IKKB) and mutant forms of the two kinases that interact with IkBα (i.e. IKKα (KM) and IKKB (KA)) (e.g. see purification and kinase assays in Examples I-III). Karin et al describe an experiment where labeled antibodies were used to assess the cellular localization of RelA in HeLa cells transfected with different plasmids encoding the different kinase proteins. Karin et al teach that expression of either of the mutant forms of the kinases leads to the inhibition of nuclear translocation of RelA in TNF-treated cells as compared to cells that do not comprise the mutant kinase proteins (i.e. inhibition of phosphorylation/degradation of IkB) (e.g. column 38, lines 5-42). Karin et al teach that IkBα and IkB are expressed in most cell types and that each IkB factor binds specifically to RelA/NF-kB dimers. The patent further teaches that phosphorylation of IkBα occurs in response to tumor necrosis factor (TNF) (e.g. column 12, lines 19-47). Thus, Karin et al teach an experiment where, in response to the presence of a "candidate agent" (i.e. IKKα (KM) and IKKB (KA)), an increased level of deacetylated RelA is detected by an increase in RelA binding to IkB. Further, the skilled artisan would recognize, based upon the combined teachings of the Karin et al patent and the instant specification, that the IkB in the NF-kB/IkB complex detected in the experiment taught by Karin et al would necessarily comprise IkBα. Moreover, the skilled artisan would recognize, based upon the teachings of both specifications, that the HeLa cells would necessarily comprise HDAC3, CBP and p300.

Because the Office does not have the facilities for examining and comparing the applicant's product with the products of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed products and the products of the prior art (e.g. that the products of the prior art do not possess the same material

structural and functional characteristics of the claimed product) **(i.e. that the IkB present in the NF-kB complex measured by Karin et al does not comprise any IkBα or that the HeLa cells of Karin et al do not comprise HDAC3, CBP or p300)**. See in re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Claims 1, 4-7, 19-22 are rejected under 35 U.S.C. 102(b) as being anticipated by Traenckner, et al (EMBO Journal, Vol. 13, No. 22, pages 5433-5441; see the entire reference). **This is a new rejection.**

Traenckner et al teach that a proteosome inhibitor, PSI (Cbz-Ile-Glut(O-t-Bu)-Ala-leucinal) prevents activation of NF-kB and stabilizes a newly phosphorylated from of IkBα that remains bound to NF-kB (e.g. the Abstract). Traenckner et al teach that PSI prevents degradation of IkBα and results in the accumulation of NF-kB (p50/p65) in HeLa cells that have been stimulated with tumor necrosis factor (TNF) (e.g. page 5434, column 2-page 5435; Figure 8).

According to applicants, NFkB does not bind IkB well when RelA is acetylated. According to Traenkner et al, the stabilized and phosphorylated form of IkB remains bound to NFkB. Therefore, in view of applicants' own model and the teachings of the Traenckner et al reference, the stabilization of IkBα in the presence of PSI relative to untreated cells observed by Traenckner et al necessarily constitutes an observation of an increase in the amount of deacetylated RelA in treated cells relative to untreated cells.

Because the Office does not have the facilities for examining and comparing the applicant's product with the products of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed products and the products of

the prior art (e.g. that the products of the prior art do not possess the same material structural and functional characteristics of the claimed product) **(i.e. the HeLa cells of Karin et al do not comprise HDAC3, CBP or p300)**. See in re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 22 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **This is a new rejection.**

Claim 22 is vague and indefinite in that the metes and bounds of the phrase "...is compared to a level of deacetylated RelA in the absence of the candidate agent and the presence of HDAC3..." are unclear. It is unclear as written whether the phrase is intended to specify that one or two comparisons are made (i.e. comparison to the level in the absence of the agent and also comparison to the level in the presence of HDAC3, or alternatively, comparison to the levels in the absence of the candidate agent but in the presence of HDAC3). Upon reading the specification, it appears the latter interpretation is correct. It would be remedial to amend the claim language to more clearly indicate the nature and the number of comparison steps to be made in practicing the claimed method.

Conclusion

Claims 1, 4-7 & 19-22 are rejected. Claims 8-10, 23-24 are objected to as being dependent upon a rejected claim. Claims 8-10, 23-24 would be allowable if rewritten in independent form comprising each of the limitations of the claims upon which they are currently dependent.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G Leffers Jr., PhD whose telephone number is (571) 272-0772. The examiner can normally be reached on 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gerald G Leffers Jr., PhD
Primary Examiner
Art Unit 1636

GERRY LEFFERS
PRIMARY EXAMINER